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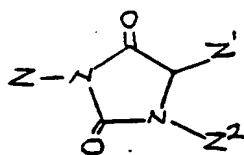
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(54) **Substituted hydantoin compounds.**

(57) **The present invention is concerned with compounds of formula (I)**



(I)

wherein

Z is C₁₋₁₂ straight or branched alkyl, C₃₋₁₂ alkenyl or alkynyl, C₆ or C₁₀ aryl, C₆ or C₁₀ aryl-C₁₋₁₂ alkyl (wherein in either case the aryl group is optionally substituted by one or more groups independently selected from phenyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, and halo) or C₄₋₈ cycloalkyl-C₁₋₁₂ alkyl;

Z' is a group of formula -CH₂-X-X'-X², wherein X is selected from -(CH₂)₂- and cis and trans -CH=CH-, X' is a covalent bond or a straight or branched alkylene chain having from 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa (-O-) or thia (-S-) provided that at least one carbon atom separates the oxa or thia group from a carboxyl or -CH=CH-group, and X² is a carboxyl group, a C₁₋₄ alkyl ester, or an amide group;

Z'' is a group selected from -NH-CH₂-R and -N=CH-R, wherein R is a group selected from -CO-Y and -CH(Y')-Y, Y being a group selected from C₁₋₈ alkyl, C₃₋₈ alkenyl, phenyl-C₁₋₄ alkyl and phenyl (wherein the phenyl group in both cases is optionally substituted by one or more groups independently selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, halo and trihalomethyl), C₄₋₈ cycloalkyl, and 5- or 6-membered heterocyclic radicals containing at least one heteroatom selected from oxygen, sulphur and nitrogen; and Y' being a group selected from hydrogen, hydroxy, C₁₋₄ alkoxy and C₂₋₅ acyloxy; and salts and solvates thereof.

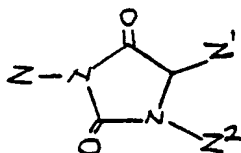
Substituted Hydantoin Compounds

This invention relates to novel substituted hydantoin derivatives suitable for use as therapeutic agents and useful as prostanoic acid receptor probes. The compounds described herein have chemical and pharmacological properties related to those of natural prostaglandins as demonstrated by their ability to antagonise the physiological effects of prostaglandin D₂ (PGD₂) in various biological preparations.

In GB-A-1595694, GB-A-1595695, GB-A-1603407 and EP-A-0126849 are described certain hydantoin derivatives which have pharmacological properties related to those of natural prostaglandins. However, none of the hydantoin derivatives described therein have specific selectivity for a particular class of prostacyclin receptors over other prostanoid receptor types.

We have now discovered a novel class of hydantoin derivatives, shown below in formula (I), which are selective antagonists of the PGD₂ DP-receptor (nomenclature of I Kennedy *et al.*, Prostaglandins, 24, 667 (1982)) and which have useful medical prophylactic and therapeutic properties for the treatment of diseases and disease conditions wherein blockade of the DP-receptor mediated effects of PGD₂ is indicated, as well as certain non-medical uses such as providing a prostanoid receptor probe specific for PGD₂ receptors which can be used in diagnostic applications.

According to a first aspect of the present invention, therefore, there is provided a compound of formula (I)



(I)

wherein

Z is C₁₋₁₂ straight or branched alkyl, C₂₋₁₂ alkenyl or alkynyl, C₆ or C₁₀ aryl, C₆ or C₁₀ aryl-C₁₋₁₂ alkyl (wherein in either case the aryl group is optionally substituted by one or more groups independently selected from phenyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, and halo) or C₄₋₈ cycloalkyl-C₁₋₁₂ alkyl;

Z¹ is a group of formula -CH₂-X-X¹-X², wherein X is selected from -(CH₂)₂- and *cis* and *trans* -CH=CH-, X¹ is a covalent bond or a straight or branched alkylene chain having from 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa (-O-) or thia (-S-) provided that at least one carbon atom separates the oxa or thia group from a carboxyl or -CH=CH-group, and X² is a carboxyl group, a C₁₋₄ alkyl ester, or an amide group;

Z² is a group selected from -NH-CH₂-R and -N=CH-R, wherein R is a group selected from -CO-Y and -CH(Y¹)-Y, Y being a group selected from C₂₋₈ alkyl, C₂₋₈ alkenyl, phenyl-C₁₋₄ alkyl and phenyl (wherein the phenyl group in both cases is optionally substituted by one or more groups independently selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, halo and trihalomethyl), C₄₋₈ cycloalkyl, and 5- or 6-membered heterocyclic radicals containing at least one heteroatom selected from oxygen, sulphur and nitrogen; and Y¹ being a group selected from hydrogen, hydroxy, C₁₋₄ alkoxy and C₂₋₈ acyloxy;

and salts and solvates thereof.

The present invention further includes biprecursors or "pro-drugs" of the compounds of the invention, namely compounds that are converted *in vivo* into compounds of formula (I) or salts or solvates thereof.

Unless the context indicates to the contrary, any reference hereinafter to a compound of formula (I) is a reference to the compound of formula (I) per se the salts and solvates thereof. When intended for administration to the human or animal body (as described further hereinbelow) such salts and solvates are those which are pharmaceutically acceptable. Furthermore, in formula (I) and throughout this specification, unless specifically stated to the contrary, alkyl groups or the alkyl part of alkyl-containing moieties such as acyl, are preferably straight or branched and contain from one to four carbon atoms. "Halo" means, in particular, chloro, bromo or iodo. When Y is a 5- or 6-membered heterocyclic radical as defined above, the ring of the radical may be saturated or unsaturated, for example, pyridyl, thienyl, tetrahydropyranyl, or tetrahydrofuryl. When Y is an aralkyl group, this may be a phenalkyl group, for example, benzyl. The above-mentioned salts may be formed from those compounds of formula (I) wherein X² is a carboxyl group. Particularly valuable salts for medical purposes are those having a physiologically acceptable cation, such as ammonium or that of an alkali metal, for example, sodium or potassium, an alkaline earth metal, for example, calcium or magnesium, or an organic base, particularly an amine such as tri(hydroxymethyl)-

aminomethane or ethanolamine. Salts having non-physiologically acceptable cations are included within the ambit of this invention as useful intermediates for the isolation or purification of the corresponding compounds of formula (I) or their physiologically acceptable salts or solvates. Except when there is clear indication to the contrary, formula (I) and other formulae in the specification embrace all stereoisomers represented therein. In particular, such formulae include geometrical isomers having the syn and anti configurations at the $-N=CH$ -group, as well as diastereoisomers and individual enantiomers and racemic mixtures of these forms.

Preferred compounds of formula (I), by virtue of their advantageous pharmacological and other properties, include those wherein:

- 10 Z is phenyl or phenyl- C_{1-3} alkyl wherein the phenyl group is optionally substituted by one or more groups independently selected from phenyl, alkyl and alkoxy;
 Z¹ is $-CH_2-X-X^1-X^2$ wherein X is $-(CH_2)_2-$, X¹ is an alkylene chain of from 2 to 4 carbon atoms and X² is a carboxyl group or a C_{1-4} alkyl ester; and
 Z² is a group selected from $-NH-CH_2-R$ and $-N=CH-R$ wherein R is a group of formula $-CH(Y^1)-Y$ wherein Y¹ is hydroxy and Y is phenyl, C_{1-3} alkyl or C_{4-6} cycloalkyl, particularly cyclohexyl;
 15 and salts and solvates thereof.

Particularly preferred compounds, including salts and solvates thereof, are 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin and 3-(p-biphenyl)-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino) hydantoin and their ethylideneamino analogues 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylideneamino)hydantoin and 3-(p-biphenyl)-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylideneamino)hydantoin. Of these, 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino) hydantoin is especially preferred by virtue of its exceptional pharmacological properties.

As indicated, the compounds of formula (I) have chemical and pharmacological properties related to those of natural prostaglandins. Specifically, the compounds of the invention antagonise some of the physiological effects of PGD_2 and are therefore particularly useful in the treatment or prophylaxis of diseases or disease conditions wherein PGD_2 is overproduced. For example, some of the symptoms exhibited by individuals having diseases or disease conditions involving mast cell dysfunction are consistent with the overproduction of PGD_2 , a compound which is known to be released by the degranulation of mast cells. Diseases or disease conditions for which the present compounds will be particularly useful therefore include those involving mast cell dysfunction, such as systemic mastocytosis and systemic mast cell activation disorders, urticaria and allergic rhinitis.

Systemic mastocytosis is a disease in which there is abnormal proliferation of tissue mast cells and extremely high plasma and urinary levels of PGD_2 and its metabolites. Patients experience episodic attacks of facial flushing, severe headache, syncope, tachycardia and, sometimes, life-threatening hypotension symptoms which are reminiscent of the effects of PGD_2 infusion in normal men.

Heat and cold induced urticaria are associated with dermal mast cell degranulation and are accompanied by itching, erythema and oedema. PGD_2 may be involved in the skin reactions mediated by mast cell degranulation either by direct action or by potentiating the effects of other mediators. Patients with allergic rhinitis also release histamine and PGD_2 into nasal secretions following challenge with antigen. The nasal stuffiness associated with this condition is the result of PGD_2 -mediated vasorelaxation.

According to a second aspect of the present invention, therefore, there is provided a compound of formula (I) for use in a method of treatment or prophylaxis of the human or animal body by therapy, particularly the treatment or prophylaxis of diseases or disease conditions wherein blockade of the DP-receptor mediated effects of PGD_2 is indicated, for example, conditions in which overproduction of PGD_2 is implicated, such as systemic mastocytosis and systemic mast cell activation disorders, urticaria and allergic rhinitis.

As also indicated, the compounds of formula (I) provide a prostanoid receptor probe which is specific for PGD_2 receptors over other prostanoid receptor types. This ability of the compounds of the invention to selectively block PGD_2 receptors finds particular utility in pharmacological assays such as those used for diagnostic purposes. For example, the present compounds may be used with advantage in research on prostaglandin mimetics other than PGD_2 where specific blockade of PGD_2 receptors is required.

According to a third aspect of the present invention, therefore, there is provided a compound of formula (I) for use as a prostanoid receptor probe specific for PGD_2 receptors.

The amount of a compound of formula (I) required to achieve the desired therapeutic effect will, of course, depend on a number of factors, for example, the specific compound chosen, the disease or disease condition for which it is intended, the mode of administration, and the recipient. In general, a daily dose may be expected to lie in the range 0.01mg to 500mg per kilogram bodyweight. For example, an intravenous dose may lie in the range 0.01mg to 100mg/kg which may conveniently be administered as an

infusion of from 1.0 μ g to 100 μ g/kg/minute. Infusion fluids suitable for this purpose may contain, for example, from 1.0 μ g to 1.0mg per millilitre.

Unit dose formulations may contain from 10 μ g to 500mg of active compound according to the mode of administration and may be administered one or more times per day separately or in multiples. Thus ampoules for injection may contain, for example, from 0.1mg to 10mg of active compound, orally administrable formulations, such as tablets or cachets, may contain, for example, from 1mg to 500mg, typically from 10mg to 100mg, and inhalational doses may contain, for example, from 0.1 μ g to 500 μ g per inhalation.

The amount of a compound of formula (I) required in a diagnostic application to specifically blockade PGD₂ receptors will, of course, depend on the particular application and on the nature of the specific compound used. Typically an aqueous solution of the compound having a concentration of from 1nM to 1 μ M is employed.

The above mentioned doses refer to the compounds of formula (I) per se; where a salt or solvate is used, the dose should be taken as referring to the corresponding anion or unsolvated compound.

According to a fourth aspect of the present invention, there is provided a pharmaceutical formulation comprising, as active ingredient, at least one compound of formula (I) and/or a pharmacologically acceptable salt or solvate thereof, together with at least one pharmaceutical carrier or excipient. These pharmaceutical formulations may be used in the treatment or prophylaxis of any of the diseases or disease conditions referred to above wherein blockade of the DP-receptor mediated effects of PGD₂ is indicated. The carrier must of course be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not be deleterious to the recipient. The carrier may be a solid or a liquid, and is preferably formulated with a compound of formula (I) as a unit dose formulation, for example, a tablet which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmacologically active substances may also be present in the formulations of the present invention, for example, histamine antagonist such as acrivastine or triprolidine. The compound of formula (I) may be incorporated in the formulations of the invention as the compound per se or as a pharmaceutically acceptable salt or solvate thereof. The formulations may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixture of components of the formulation.

Formulations of the invention include those suitable for administration by oral, buccal (eg sub-lingual), parenteral (eg subcutaneous, intramuscular, or intravenous), or rectal routes, by topical application, or by nasal/buccal inhalation. In any given case, the most suitable mode of administration will depend on the nature and severity of the condition being treated and on the nature of the active compound used.

Formulations suitable for oral administration may be presented as discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous non-aqueous liquids; as oil-in-water emulsions; or as water-in-oil emulsions. Such formulations may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with a carrier which comprises one or more appropriate ingredients. In general, the formulation may be prepared by uniformly and intimately admixing the active ingredient with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compressing or moulding a powder or granules of the active ingredient, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form, such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, or surface active/dispersing agent(s). Moulded tablets may be made by moulding in a suitable machine the powdered active ingredient moistened with an inert liquid diluent.

Formulations suitable for buccal (eg sub-lingual) administration include lozenges comprising the active ingredient in a flavoured base, eg sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active ingredient, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous or intramuscular injection. Such preparations may conveniently be prepared by admixing the active ingredient with water and rendering the product sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing the active ingredient with one or more conventional solid carriers forming the suppository base, for example, cocoa butter, and shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used in such formulations include petroleum

jelly, lanolin, polyethylene glycols, alcohols and combinations thereof. The active ingredient is generally present in a concentration of from 0.1% to 15% w/w of the composition, for example, from 0.5% to 2%.

Formulations suitable for nasal/buccal inhalation include compositions consisting of particles containing active ingredient which can be delivered into the lungs of the patient. Such compositions are conveniently in the form of a dry powder for administration from a powder inhalation device or self-propelling powder-dispensing container, for example, a self-propelling aerosol composition in a sealed container. Preferably, the powder comprises particles of which at least 98% by weight have a diameter of greater than $0.5\mu\text{m}$ and at least 95% by number have a diameter of less than $7\mu\text{m}$. Most desirably, at least 95% by weight of the particles have a diameter of greater than $1\mu\text{m}$ and at least 90% by number have a diameter less than $6\mu\text{m}$. Compositions in the form of dry powders preferably include a solid fine powder diluent, such as sugar, and are conveniently presented in a pierceable capsule, for example, of gelatin.

Self-propelling compositions in accordance with the invention may be either powder-dispensing compositions or compositions dispensing the active ingredient in the form of droplets of a suspension. Self-propelling powder-dispensing compositions typically includes a liquid propellant having a boiling point of below 18°C at atmospheric pressure. Generally the propellant may constitute 50% to 99.9% w/w of the composition whilst the active ingredient may constitute from 0.1% to 20% w/w, of the composition, for example, about 2% w/w. The carrier in such compositions may include other constituents, in particular a liquid non-ionic or solid anionic surfactant, or a solid diluent (preferably having a particle size of the same order as the particles containing the active ingredient) or both. The surfactant may constitute from 0.01% up to 20% w/w of the composition, though preferably below 1% w/w.

Self-propelling compositions wherein the active ingredient is present in solution comprise an active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. The co-solvents may constitute 5% to 40% w/w of the composition, though preferably less than 20% w/w.

Compositions of the present invention may also be in the form of an optionally sterile aqueous or dilute alcoholic solution of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. Such formulations usually contain a flavouring agent, such as saccharin sodium, and a volatile oil. A buffering agent and a surface active agent may also be included in such a formulation, together with a preservative such as methylhydroxybenzoate.

Other formulations suitable for nasal administration include a coarse powder having a particle size of from $20\mu\text{m}$ to $500\mu\text{m}$ which is administered in the manner in which snuff is taken, ie by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

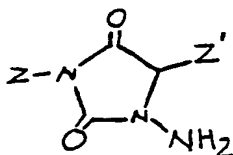
In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants), emulsifying agents, and the like. Any other therapeutic ingredient may comprise one or more of the following: antibiotic (eg anti-bacterial), anti-fungal and anti-viral agents, and anti-histamines (particularly peripherally acting anti-histamines). However, when such other agent(s) are also present, the compound of formula (I) or physiologically acceptable salt or solvate thereof and the other agent(s), need not necessarily be present as a pharmaceutical formulation as hereinbefore defined, but merely in combination or intimate admixture, ie a pharmaceutically acceptable carrier need not be present.

According to a fifth aspect of the present invention, therefore, there is provided the use of a compound of formula (I) in the preparation of an agent for use in the treatment or prophylaxis of diseases or disease conditions wherein blockade of the DP-receptor mediated effects of PGD_2 is indicated.

The compounds of formula (I) may be prepared by any conventional manner, and, in accordance with the present invention, may, for example, be prepared by any method hereinafter described.

Thus according to a sixth aspect of the present invention, we provide a process for the preparation of compounds of formula (I) which comprises

(a) for the preparation of hydantoins wherein Z^2 is $-\text{N}=\text{CH}-\text{R}$, wherein R is as defined above, reacting a compound of formula (II) with a compound of formula (III)

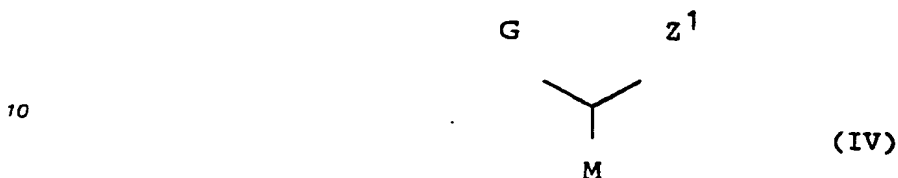


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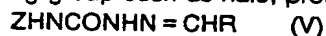
wherein Z, Z¹ and R are as defined above, in, for example, the presence of base and a suitable solvent, such as methanol;

(b) for the preparation of hydantoin wherein Z² is -N=CH-R, wherein R is as defined above, reacting a compound of formula (IV)

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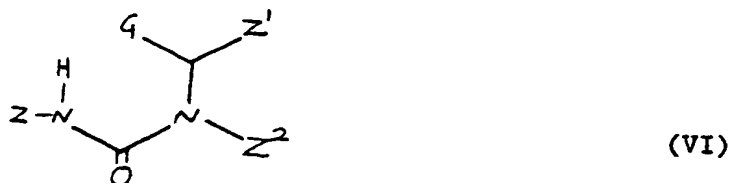
15 wherein Z¹ is as defined above, G is carboxy or a derivative thereof, such as an amide derivative, for example, carbamoyl, or an ester thereof, particularly a C₁₋₄ alkyl ester thereof, or G is cyano, and M is a leaving group such as halo, preferably bromo, with a compound of formula (V)



20 wherein R and Z are as defined above, in the presence of base in a polar solvent, such as ethanol;

(c) for the preparation of hydantoin wherein Z² is -N=CH-R, wherein R is as defined above, cyclising a compound of formula (VI)

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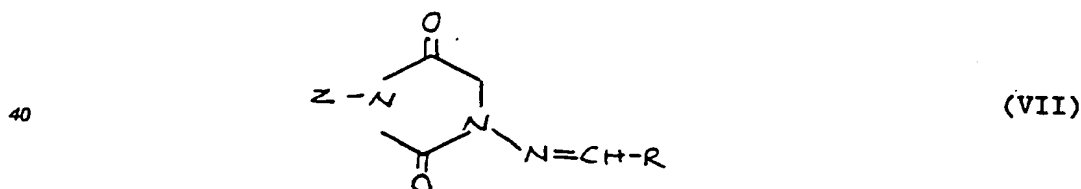


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wherein G, Z, Z¹ and Z² are as defined above, in, for example, the presence of acid or base or by heating in an inert solvent;

(d) for the preparation of hydantoin wherein Z² is -N-CH=R, wherein R is as defined above, treating a compound of formula (VII)

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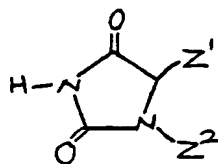
45 wherein R is as defined above, with methyl magnesium carbonate followed by reaction in the presence of base with a compound of formula (VIII)



50 wherein M and Z¹ are as defined above, in a non-protic solvent, such as THF or ether;

(e) reacting a compound of formula (IX) with a compound of formula (X)

55



(IX)

wherein Z^1 and Z^2 are as defined above, L is a suitable leaving group, such as halo (eg bromine) or hydroxy, and Z^3 is defined as for Z above (other than C_6 or C_{10} aryl) or an alternative imino protecting group, for example, benzylideneamino ($-N=CH-Ph$), in the presence of base and, when L is hydroxy, triphenylphosphine and diethylazodicarboxylate (Mitsunobu, Tetrahedron Letters (1972) 1279); and subsequently, if desired, effecting one or more of the following optional conversions in any desired order:

- (i) wherein a hydantoin of formula (I) is formed and an ester, converting said ester into the corresponding acid or a salt or solvate amide thereof;
- (ii) where a hydantoin of formula (I) is formed and is an acid, converting said acid into the corresponding ester or a salt or solvate thereof;
- (iii) where a hydantoin of formula (I) is formed wherein Z is hydrogen, converting said hydantoin into a corresponding hydantoin wherein Z is alkyl;
- (iv) where a hydantoin of formula (I) is formed wherein R is $-CH(Y^1)Y$, wherein Y^1 is an acyloxy group and Y is as defined above, converting said hydantoin into a corresponding hydantoin of formula (I) wherein Y^1 is a hydroxy group;
- (v) where a hydantoin of formula (I) is formed wherein R is $-CO-Y$, converting said hydantoin into a corresponding hydantoin wherein R is $-CH(OH)-Y$; or
- (vi) where a hydantoin of formula (I) is formed wherein Z^2 is $-N=CH-R$, converting said hydantoin into a corresponding hydantoin wherein Z^2 is $-NH-CH_2-R$, wherein R is as defined above.

The reaction of process (a) may conveniently be performed in a suitable solvent, for example, methanol.

The reaction of process (b) may conveniently be carried out by heating in the presence of a suitable base, such as an alkali metal alkoxide, for example, sodium ethoxide, and optionally in the presence of a suitable solvent, such as ethanol;

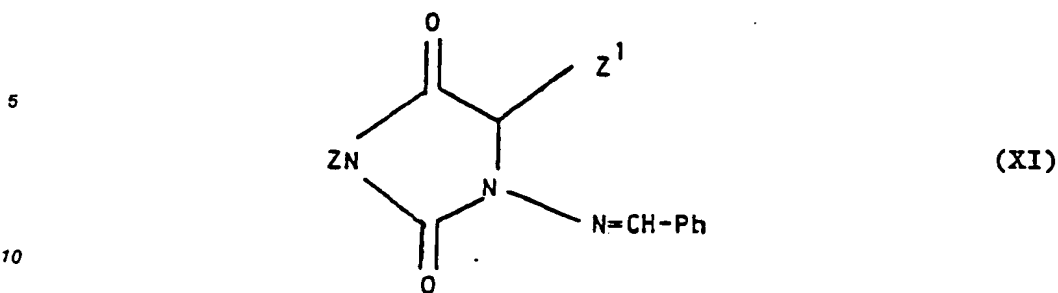
In process (c), the carboxyl derivative may, for example, be an amide or ester, in particular, an alkyl ester. The cyclisation may be performed under acidic conditions or by heating alone. The reaction may be effected in the absence of a solvent or an inert solvent may be used, for example, a hydrocarbon solvent, such as petrol. Alternatively, where G is alkoxycarbonyl, cyclisation may be effected in the presence of a suitable base, for example, an alkoxide, such as sodium ethoxide.

In process (d), the compound of formula (VI) may be in a suitable solvent, such as dimethylformamide.

In process (e), where L is selected from halo, then the compound of formula (IX) may preferably be metalated, for example, by reaction of a compound of formula (IX) with sodium hydride in a suitable solvent, for example, dimethylsulphoxide. Where L is a hydroxy group, so that the compound of formula (IX) is an alcohol, process (e) may employ known conditions for such substitution, for example, the presence of other reagents, such as triphenylphosphine and diethylazodicarboxylate.

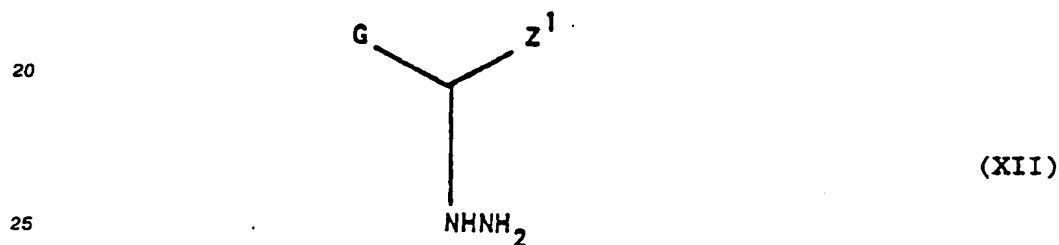
If, in the above general processes, it is desired separately isolate one or both diastereoisomers of a compound of formula (I) in the case where an appropriate compound exists in mixed isomeric form, separation of the isomers may conveniently be performed in conventional manner, for example, by h.p.l.c. or by preferential crystallisation.

Compounds of formula (II) may be prepared by hydrogenation of a compound of formula (XI)



wherein Z and Z¹ are as defined above and Ph represents phenyl, under suitable conditions. Conveniently, such hydrogenation may be performed at elevated pressure in the presence of a palladium/charcoal catalyst. If desired, the reaction may be carried out with heating.

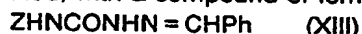
Compounds of formula (II) may also be prepared by reaction of a compound of formula (XII)



wherein G is as defined above, with an isocyanate compound Z-NCO, wherein Z is as defined above. The reaction may proceed in the absence of a solvent, but desirably an inert solvent is used which is preferably polar, such as water or a mixture of water with acetone, dimethylformamide, dimethylsulphoxide, or a lower alkanol, such as ethanol, or a hydrocarbon solvent, an ether, or a halogenated hydrocarbon solvent, such as chloroform. When desired, for example, if no solvent is used, the reaction may be promoted by heating the reactants.

Instead of using isocyanate, a compound of formula (X) may be reacted with a suitable urea derivative. A solvent is not essential, but, if desired, an inert solvent, such as one of those mentioned above, may be used; the reaction is preferably effected at an elevated temperature, for example, from 100° to 125°C, but temperatures of up to 150°C may be used.

Compounds of formula (XI) may be prepared by reaction of a compound of formula (IV), as previously defined, with a compound of formula (XIII)



wherein Z is as defined above and Ph represents phenyl.

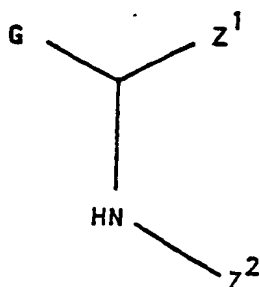
Compounds of formulae (V) and XIII) may be prepared, for example, by reaction of the appropriate aldehyde with semicarbazide, if necessary under mildly acidic conditions.

Compounds of formula (IV) may conveniently be prepared in a manner analogous to that described by Schwank and Papa in J.Amer.Chem.Soc. (1948) 70, 3626.

Compounds of formula (XII) may be prepared by the reaction of a compound of formula (IV), as previously defined, with an excess of hydrazine hydrate under appropriate conditions, in a suitable solvent such as ethanol.

Compounds of formula (III) may be prepared in a manner analogous to that described, for example, by Tiffany *et al* in J.Amer.Chem.Soc. (1957) 79, 1682, or by Royals and Robinson in J.Amer.Chem.Soc. (1956) 78, 4161.

Compounds of formula (VI) may be prepared by reaction of a compound of formula (XIV)

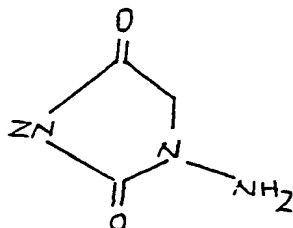


(XIV)

wherein G, Z¹ and Z² are as defined above, with an isocyanate compound Z-NCO, wherein Z is as defined above. The reaction may be performed in a manner, and under conditions, analogous to those previously described for the conversion of a compound of formula (XII) to a compound of formula (II). In the synthesis, the compound of formula (VI) need not be isolated from the reaction mixture and may be converted directly to a compound of formula (I) under the described reaction conditions.

Compounds of formula (XIV) may conveniently be prepared by the reaction of a compound of formula (XII), as previously defined, with a compound of formula (III), as previously defined, under reaction conditions analogous to those described for process (a).

Compounds of formula (VII) may be prepared by the reaction of a compound of formula (XV)



(XV)

with a compound of formula (III), as previously defined, by conventional means.

Compounds of formula (XV) may be prepared according to the method described by D Jack in J.Pharm.Pharmacol. (1959) 108T and, where appropriate, alkylating the ring at the 3-position in a conventional manner.

Compounds of formula (VIII) or (X) may, for example, be prepared in a manner analogous to that described by D E Ames *et al* in J. Chem.Soc. (1950) p.174. Compounds of formula (IX) may be prepared by the method described in EP-A-0126849.

In optional conversion (i) above, the reaction is advantageously effected by hydrolysis, for example, under basic conditions, such as in the presence of sodium hydroxide. A similar hydrolysis may be employed in optional conversion (iii) where a Y¹ acyloxy group is converted into a Y¹ hydroxy group.

In optional conversion (ii), the reaction is advantageously effected by treatment with the appropriate alcohol, for example ethanol, in the presence of a suitable acid, such as sulphuric acid.

After either of conversions (i) or (ii), the appropriate carboxylate salt may be formed by treatment of the acid with an appropriate inorganic or organic base in an appropriate solvent, such as water, followed by isolation, for example, by methanol precipitation, evaporation, or freeze-drying.

In conversion (iii), the reaction is advantageously effected by treatment with a suitable alkylating agent, such as an alkyl halide, for example, the iodide, in the presence of a suitable base, such as sodium hydroxide.

In conversion (iv), deacylation may be performed by conventional means, for example, by treatment with sodium hydroxide.

Conversion (v) may be effected by conventional reduction using an agent such as sodium borohydride under basic conditions.

In optional conversion (vi), the reaction may be effected using any appropriate reducing agent, such as the borohydride or cyanoborohydride of an alkali metal, for example, sodium or lithium. The reaction proceeds under suitable conditions which may, in the case of cyanoborohydrides, require the presence of an acid, for example, acetic acid.

In general, the reactions and conversions specified above may be effected by conventional means

using techniques known for the preparation of analogous compounds.

Intermediate compounds of formulae (II), (V), (VI), (VII), (X), (XI), (XIII) and (XV) represent further aspects of the invention.

5 In all of the foregoing chemical procedures, it is, of course, evident that the choice of reactants will be dictated in part by the functional groups present in the substrates, and, where necessary, reactants having an appropriate selectivity of action must be used.

The following Examples illustrate the invention. In the Examples, reference will be made to various compounds whose structures and exemplary preparative interrelationship are shown in Chart I.

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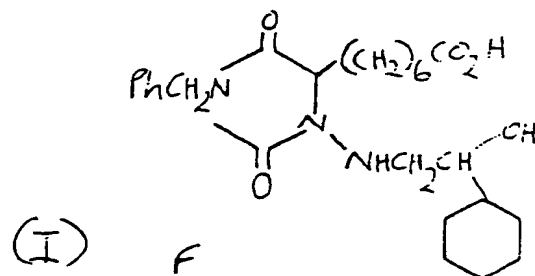
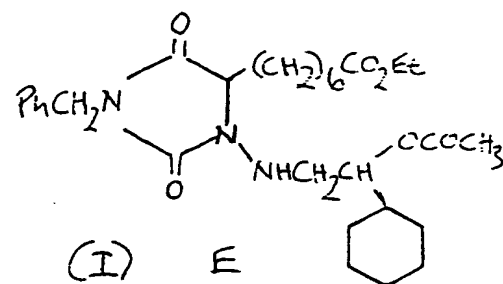
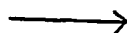
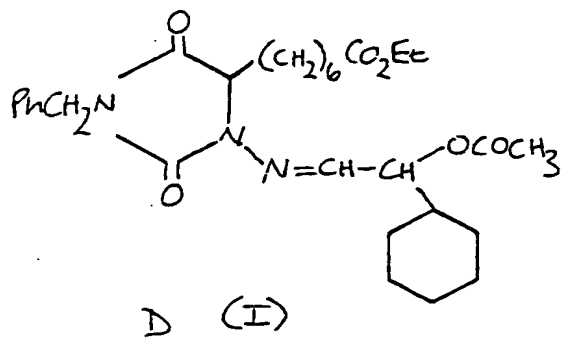
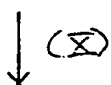
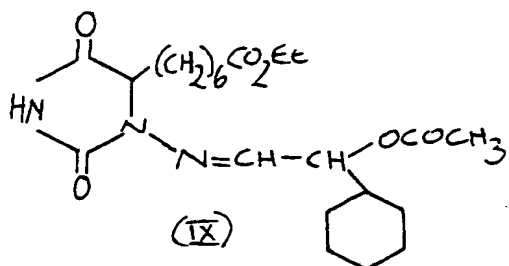
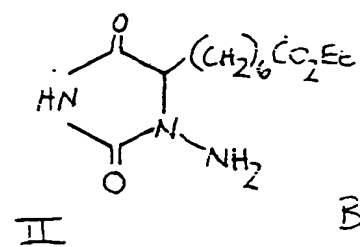
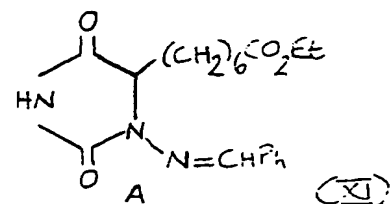
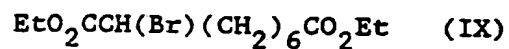
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Chart I



Example 13-Benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylidene-amino)hydantoin (Compound D)(a) 1-Benzylideneamino-5-(6-ethoxycarbonylhexyl)hydantoin (Compound A)

A solution of sodium ethoxide was prepared by dissolving sodium (4.6g) in ethanol (100ml). A suspension of benzaldehyde semicarbazone (16.3g) in the sodium ethoxide solution (50ml) and ethanol (20ml) was refluxed for 15 minutes. Diethyl 2-bromononanedioate (16g) was added and the mixture was refluxed for 30 minutes. Sodium ethoxide solution (25ml) was added and the mixture was refluxed for 5 minutes before the addition of the bromodiester (8g), followed by 30 minutes' refluxing. The remaining sodium ethoxide solution (25ml) and bromodiester (8g) were then added and the mixture was refluxed for 1 hour. Most of the ethanol was evaporated in vacuo and the residue was shaken with dilute hydrochloric acid and ether. Unchanged benzaldehyde semicarbazone (5.4g) was filtered off and the ether solution was washed with water, dried (MgSO₄) and evaporated. The semi-solid residue was treated with a small volume of ether to give 1-benzylideneamino-5-(6-ethoxycarbonylhexyl)hydantoin (13.0g) which crystallised from cyclohexane in colourless needles, m.p. 92-94°C.

(b) 1-Amino-5-(6-ethoxycarbonylhexyl)hydantoin (Compound B)

The above benzylideneamino compound (5.8g) in solution in ethanol (100ml) was hydrogenated at 10 atmospheres' pressure and 50°C in the presence of 10% palladium/charcoal catalyst for 1 hour. The catalyst was filtered off and the solvent was evaporated to leave the amino compound (4.3g) which crystallised from ethyl acetate/light petroleum (b.p. 60-80°C) as colourless needles, m.p. 80-82°C.

(c) 1-(2-Acetoxy-2-cyclohexylethylideneamino)-5-(6-ethoxycarbonyl hexyl)hydantoin (Compound C)

A solution of 1-amino-5-(6-ethoxycarbonylhexyl)hydantoin (3.0g) and 2-acetoxy-2-cyclohexylacetaldehyde (Ross *et al.*, J.Med.Chem. (1979) 22, 412) (2.24g) in methanol (20ml) was refluxed for 1 hour. The methanol was evaporated, the residue was dissolved in ether and the ether solution was washed with 1N hydrochloric acid, then water, and dried. The oil remaining after evaporation of the ether was purified by chromatography on a column of silica using a mixture of chloroform and methanol (40:1) as eluant to give a colourless oil (4.9g) showing two spots, R_f 0.46 and R_f 0.50 on t.l.c. (silica; chloroform-methanol-acetic acid (95:4:1)). Separation of a portion (1.5g) by h.p.l.c. (silica; dichloromethane-methanol-acetic acid (98.5:1.0:0.5)) gave the individual diastereoisomers of 1-(2-acetoxy-2-cyclohexylethylideneamino)-5-(6-ethoxycarbonylhexyl) hydantoin as colourless viscous oils, R_f 0.50 (625mg) and R_f 0.46 (850mg).

(d) 3-Benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexyl ethylideneamino)hydantoin (Compound D)

A solution of 5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylidene amino)hydantoin (868mg), benzyl alcohol (160mg) and triphenylphosphine (530mg) in tetrahydrofuran was treated with diethylazodicarboxylate (0.34 ml) at 15°C under an atmosphere of nitrogen. After stirring for 20 hours, the solvent was removed in vacuo and the mixture purified by column chromatography (silica gel). Eluting with chloroform gave 3-benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylideneamino)hydantoin (880mg).

¹H nmr (CDCl₃/delta): 3-benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylideneamino)-hydantoin 8.2 (1H, N-CH); 7.3 (5H, Ph); 5.1 (1H, CH (OAc)); 4.7 (2H, CH₂Ph); 2.05 (3H, COCH₃).

Example 2

3-Benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylamino) hydantoin (Compound E)

A solution of 3-benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylideneamino)hydantoin (490mg) in ethanol (5 ml) containing acetic acid (1ml) was treated at 15°C with sodium cyanoborohydride (72mg). After 20 hours, the solvent was removed in vacuo, water (20 ml) was added and the product extracted into chloroform (20 ml). The extract was dried over magnesium sulphate, filtered and concentrated.

Column chromatography (silica gel: diethyl ether/light petroleum, 1:1) gave 3-benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylamino) hydantoin (440mg). ¹H nmr (CDCl₃/delta): 7.3 (5H, Ph); 4.8 (1H, CH (OAc)); 4.6 (2H, CH₂Ph); 4.3 (1H, NH); 4.1 (2H, CO₂Et); 3.4-2.9 (2H, N-CH₂).

Example 33-Benzyl-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino) hydantoin (Compound F)

A solution of 3-benzyl-5-(6-ethoxycarbonylhexyl)-1-(2-acetoxy-2-cyclohexylethylamino)hydantoin (440mg) in ethanol (20 ml) was treated by the dropwise addition of sodium hydroxide (0.2N, 5 ml). After stirring at 10°C for 20 hours, the solution was concentrated in vacuo, water (20 ml) was added and the mixture acidified with hydrochloric acid (0.2N). The product was extracted into diethyl ether (20 ml). After drying over magnesium sulphate, filtration and concentration in vacuo gave 3-benzyl-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino)hydantoin (450mg).

¹H nmr (CDCl₃/delta): 7.3 (5H, Ph); 4.6 (2H, CH₂Ph); 4.0 (1H, CHN); 3.4 (1H, CH(OH)); 3.0 and 2.8 (1H each, NH-CH₂).

Example 43-(4-Phenylbenzyl)-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino) hydantoin

By analogy with the combined procedures of Examples 1, 2 and 3, the above compound was prepared. ¹H nmr (CDCl₃/delta): 7.5 (9H, m, Ph-Ph); 4.7 (2H, s, CH₂Ph); 4.0 (1H, t, CHN).

Example 53-(Cyclohexylmethyl)-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethyl amino)hydantoin

By analogy with the combined procedures of Examples 1, 2 and 3, the above compound was prepared. ¹H nmr (CDCl₃/delta): 4.0 (1H, t, CHN); 3.3 (2H, m, CH₂N).

Example 63-Pentyl-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino) hydantoin

By analogy with the combined procedures of Examples 1, 2 and 3, the above compound was prepared. ¹H nmr (CDCl₃/delta): 6.0 (3H, brs, exchangeable H); 4.0 (1H, t, CHN); 3.4 (3H, m, CH₂N, (1/2)CH₂NH); 0.9 (3H, t, CH₃).

Example 73-(Prop-2-enyl)-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino) hydantoin

By analogy with the combined procedures of Examples 1, 2 and 3, the above compound was prepared. ¹H nmr (CDCl₃/delta): 6.0-5.0 (3H, m, CH₂=CH); 4.1 (3H, m, CH₂N and CHN); 3.3 (1H, m, OCH); 2.9 (2H, m, CH₂NH); 2.3 (2H, t, CH₂CO₂).

Example 83-(Prop-2-ynyl)-5-(6-carboxyhexyl)-1-(2-hydroxy-2-cyclohexylethylamino) hydantoin

5 By analogy with the combined procedures of Examples 1, 2 and 3, the above compound was prepared.
¹H nmr (CDCl₃/delta): 4.3 (2H, m, CH₂N); 4.0 (1H, t, CHN).

Biological Activity

10 Antagonism of the effects of PGD₂ and 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin, a known PHD₂ analogue hereinafter referred to as "compound A", by the compounds of Examples 3 to 6 was studied in human washed platelets and rabbit jugular vein.

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1. Washed human platelets

Washed platelet suspensions were prepared according to a modified version of the method of Vargas et al (Prostaglandins (1982) 23, 929). The suspension was then stored at 4°C for 2 hours and, before use, the
 20 following additions were made: Ca⁺⁺, 1μM, indomethacin, 5mcg ml⁻¹; and fibrinogen, 400 mcg ml⁻¹. Aggregation responses were measured using 0.5ml aliquots of the suspension maintained at 37°C and stirred with a metal bar at 900 r.p.m. in 300 BD-S Payton dual channel aggregometers and recorded on Gould BS 272 pen recorders.

Inhibition of platelet aggregation by PGD₂ and compound A were studied as follows. The prostaglandin
 25 receptor agonists were incubated in the platelet suspension for 6 minutes prior to adding ADP (5 × 10⁻⁶M). The reproducibility of the ADP-induced aggregation response was checked at intervals throughout the experiment. Antagonists were added 2 minutes before the agonist. Responses were expressed as percent inhibitions of the standard ADP-induced aggregation.

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2. Rabbit jugular vein

Vascular smooth muscle relaxation in response to PGD₂ and compound A was measured as changes in isometric force. Isolated ring segments of rabbit jugular vein suspended in Kreb's buffer, gassed with 95%
 35 O₂/5% CO₂ and maintained at 37°C, were treated with: indomethacin, 1 μg ml⁻¹, and the stable thromboxane receptor antagonist BM13177 (Patscheke et al, Biomed. Biochem. Acta (1984) 43, 5321), 30μM. The experiments followed a paired curve design.

Initially, the jugular vein ring segments were subjected to a force of 0.75g, then allowed to stabilize for a period of 60 minutes during which time the preparations were washed three times. Subsequently histamine
 40 (10⁻⁶M) was added to produce tone. After establishing a stable contraction, relaxation/concentration effect curves were obtained using prostaglandin receptor agonists. Responses were expressed as per cent relaxations of the histamine-induced force. The preparations were then washed thoroughly and allowed to re-stabilise. The antagonists were then incubated for 60 minutes prior to constriction with histamine (10⁻⁶M), followed by a second determination of the prostaglandin agonist concentration effect curve.

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Analysis of Data

Measurement of antagonist affinity (pK_B) was by Schild analysis.

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Results

The results shown in the Table 1 demonstrate that the compounds of Examples 3 to 6 all behave as
 55 antagonists at the PGD₂ receptor on the human platelet.

In particular, the compound of Example 3, the preferred compound of the invention, behaves as a simple competitive antagonist of PGD₂ and compound A in the human washed platelet assay. The shifts of the anti-aggregatory concentration effect curves for PGD₂ and compound A accord with a Schild plot slope

of unity and a pK_B of 9.26. Inhibition of platelet aggregation by PGD_2 and compound A and inhibition of the relaxation effects of PGD_2 and compound A in the rabbit jugular vein were antagonised with similar potencies. The compound of Example 3 can therefore be classified as a DP-receptor antagonist. Actions of the compound at prostaglandin receptors other than DP were not observed at concentrations up to $1000\times$ greater than that required for DP receptor affinity.

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<u>Example No</u>	<u>pK_B</u>
3	9.26
4	10.0
5	8.5
6	8.5

Table 1 - Estimates of equilibrium dissociation constants at the PGD_2 receptor in human washed platelets

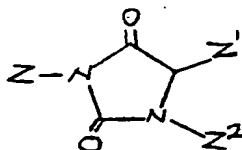
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Claims

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1. A compound of formula (I)

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(I)

wherein

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Z is C_{1-12} straight or branched alkyl, C_{2-12} alkenyl or alkynyl, C_6 or C_{10} aryl, C_6 or C_{10} aryl- C_{1-12} alkyl (wherein in either case the aryl group is optionally substituted by one or more groups independently selected from phenyl, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, and halo) or C_{4-8} cycloalkyl- C_{1-12} alkyl;

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Z¹ is a group of formula $-CH_2-X-X^1-X^2$, wherein X is selected from $-(CH_2)_2-$ and *cis* and *trans* $-CH=CH-$, X¹ is a covalent bond or a straight or branched alkylene chain having from 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa ($-O-$) or thia ($-S-$) provided that at least one carbon atom separates the oxa or thia group from a carboxyl or $-CH=CH-$ group, and X² is a carboxyl group, a C_{1-4} alkyl ester, or an amide group;

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Z² is a group selected from $-NH-CH_2-R$ and $-N=CH-R$, wherein R is a group selected from $-CO-Y$ and $-CH-(Y^1)-Y$, Y being a group selected from C_{1-4} alkyl, C_{2-4} alkenyl, phenyl- C_{1-4} alkyl and phenyl (wherein the phenyl group in both cases is optionally substituted by one or more groups independently selected from C_{1-4} alkyl, C_{1-4} alkoxy, nitro, halo and trihalomethyl), C_{4-8} cycloalkyl, and 5- or 6-membered heterocyclic radicals containing at least one heteroatom selected from oxygen, sulphur and nitrogen; and Y¹ being a group selected from hydrogen, hydroxy, C_{1-4} alkoxy and C_{2-6} acyloxy; and salts and solvates thereof.

2. A compound of formula (I) as claimed in claim 1, wherein

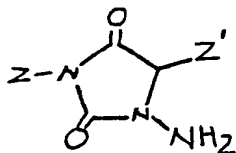
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Z is phenyl or phenyl- C_{1-3} alkyl wherein the phenyl group is optionally substituted by one or more groups independently selected from phenyl, alkyl and alkoxy;

Z¹ is $-CH_2-X-X^1-X^2$ wherein X is $-(CH_2)_2-$, X¹ is an alkylene chain or 2 to 4 carbon atoms and X² is a carboxyl group or a C_{1-4} alkyl ester; and

Z² is a group selected from -NH-CH₂-R and -N=CH-R wherein R is a group of formula -CH(Y¹)-Y in which Y¹ is hydroxy and Y is phenyl, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl, particularly cyclohexyl; and salts and solvates thereof.

3. A compound of formula (I) as claimed in claim 1, which compound is selected from
 - 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino) hydantoin;
 - 3-(p-biphenyl)-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino) hydantoin;
 - 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxy ethylidene amino)hydantoin; and
 - 3-(p-biphenyl)-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxy ethylidene amino)hydantoin;
 and salts and solvates thereof.
4. A compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, for use in human medical therapy.
5. A compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, for use in the prophylaxis or treatment of a clinical condition wherein blockade of the DP₂-receptor mediated effects of pGD₂ is indicated.
6. A compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, for use in the prophylaxis or treatment of a clinical condition associated with an overproduction of PGD₂.
7. A compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, for use in the prophylaxis or treatment of a clinical condition which involves mast cell disfunction.
8. A compound of formula (I) as claimed in any of claims 5 to 7, wherein the clinical condition is systemic mastocytosis or a systemic mast cell activation disorder, urticaria, or allergic rhinitis.
9. A compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, for use as a prostanoid receptor probe specific for pGD₂ receptors.
10. Use of a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a therapeutic agent for the prophylaxis or treatment of a clinical condition wherein blockade of the DP₂-receptor mediated effects of PGD₂ is indicated.
11. Use of a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a therapeutic agent for the prophylaxis or treatment of a clinical condition associated with an overproduction of PGD₂.
12. Use of a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a therapeutic agent for the prophylaxis or treatment of a clinical condition which involves mast cell disfunction.
13. Use of a compound of formula (I) as claimed in any of claims 10 to 12, wherein the clinical condition is systemic mastocytosis or a systemic mast cell activation disorder, urticaria, or allergic rhinitis.
14. Use of a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a reagent which is suitable as a prostanoid receptor probe specific for PGD₂ receptors.
15. A pharmaceutical formulation comprising a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, one or more pharmaceutically acceptable carriers and/or excipients therefor, and, optionally, one or more other therapeutic ingredients.
16. A process for the preparation of a compound of formula (I) as claimed in any of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, which process comprises
 - (a) for the preparation of hydantoins wherein Z² is -N=CH-R, wherein R is as defined above, reacting a compound of formula (II) with a compound of formula (III)

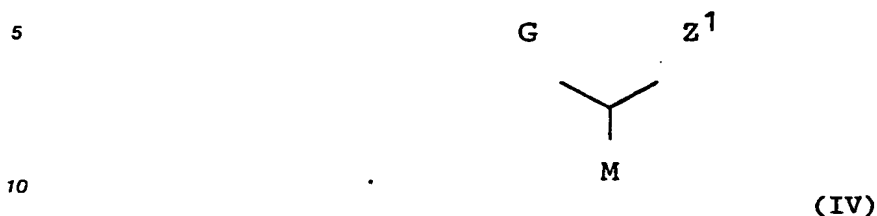


R-HCO (III)

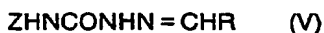
(II)

wherein Z, Z¹ and R are as defined above, in, for example, the presence of a base and a suitable solvent, such as methanol;

(b) for the preparation of hydantoin where in Z^2 is $-NH=CH-R$, wherein R is as defined above, reacting a compound of formula (IV)

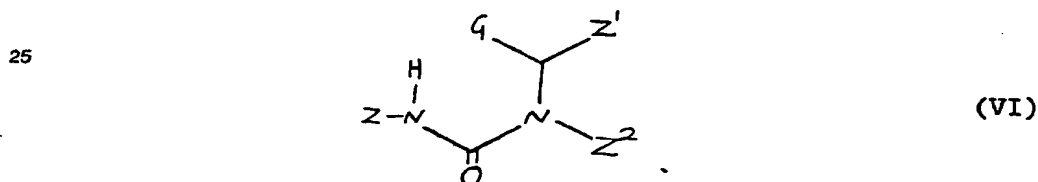


wherein Z^1 is as defined above, G is carboxy or a derivative thereof, such as an amide derivative, for example, carbamoyl, or an ester thereof, particularly a C₁₋₄ alkyl ester thereof, or G is cyano, and M is a leaving group, such as halo, preferably bromo, with a compound of formula (V)



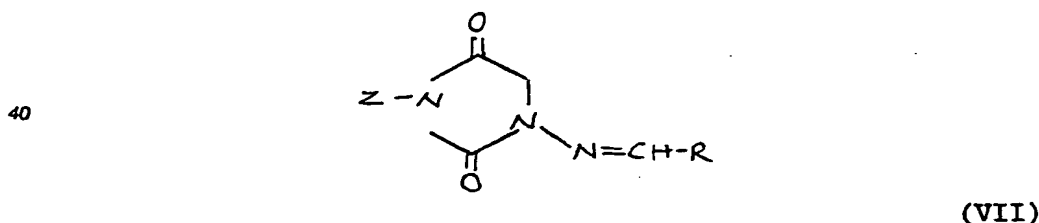
wherein R and Z are as defined above, in the presence of base in a polar solvent, such as ethanol;

20 (c) for the preparation of hydantoin wherein Z is $-N=CH-R$, wherein R is as defined above, cyclising a compound of formula (VI)



wherein G, Z, Z^1 and Z^2 are as defined above, in, for example, the presence of acid or base or by heating in an inert solvent;

(d) for the preparation of hydantoin wherein Z^2 is $-N=CH-R$, wherein R is as defined above, treating a compound of formula (VII)



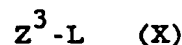
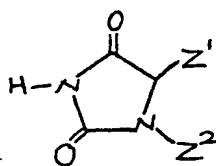
wherein R is as defined above, with methyl magnesium carbonate followed by reaction in the presence of base with a compound of formula (VIII)



wherein M and Z^1 are as defined above, in a non-protic solvent, such as THF or ether;

(e) reacting a compound of formula (IX) with a compound of formula (X)

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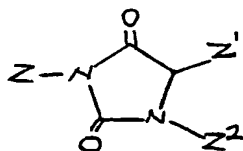
(IX)

wherein Z^1 and Z^2 are as defined above, L is a suitable leaving group, such as halo (eg bromine) or hydroxy, and Z^3 is defined as for Z above (other than C_6 or C_{10} aryl) or an alternative imino protecting group, for example, benzylideneamino ($-N=CH-Ph$), in the presence of base and, when L is hydroxy, triphenylphosphase and diethylazodicarboxylate; and subsequently, if desired, effecting one or more of the following optional conversions in any desired order:

- i) where a hydantoin of formula (I) is formed and is an ester, converting said ester into the corresponding acid or a salt or solvate thereof;
- ii) where a hydantoin of formula (I) is formed and is an acid, converting said acid into the corresponding ester or a salt or solvate thereof;
- iii) where a hydantoin of formula (I) is formed wherein Z is hydrogen, converting said hydantoin into a corresponding hydantoin wherein Z is alkyl;
- iv) where a hydantoin of formula (I) is formed wherein R is $-CH(Y^1)Y$, wherein Y^1 is an acyloxy group and Y is as defined above, converting said hydantoin into a corresponding hydantoin of formula (I) wherein Y^1 is a hydroxy group;
- v) where a hydantoin of formula (I) is formed wherein R is $-CO-Y$, converting said hydantoin into a corresponding hydantoin wherein R is $-CH(OH)-Y$; or
- vi) where a hydantoin of formula (I) is formed wherein Z^2 is $-N=CH-R$, converting said hydantoin into a corresponding hydantoin wherein Z^2 is $-NH-CH_2-R$, wherein R is as defined above.

Claims for the following Contracting States: SP, GR

1. A process for the preparation of a compound of formula (I)



(I)

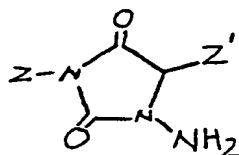
wherein

Z is C_{1-12} straight or branched alkyl, C_{1-12} alkenyl or alkynyl, C_6 or C_{10} aryl, C_6 or C_{10} aryl- C_{1-12} alkyl (wherein in either case the aryl group is optionally substituted by one or more groups independently selected from phenyl, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, and halo) or C_{4-6} cycloalkyl- C_{1-12} alkyl;

Z^1 is a group of formula $-CH_2-X-X^1-X^2$, wherein X is selected from $-(CH_2)_2-$ and cis and trans $-CH=CH-$, X^1 is a covalent bond or a straight or branched alkylene chain having from 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa ($-O-$) or thia ($-S-$) provided that at least one carbon atom separates the oxa or thia group from a carboxyl or $-CH=CH$ -group, and X^2 is a carboxyl group, a C_{1-4} alkyle ester, or an amide group;

Z^2 is a group selected from $-NH-CH_2-R$ and $-N=CH-R$, wherein R is a group selected from $-CO-Y$ and $-CH-(Y^1)-Y$, Y being a group selected from C_{1-4} alkyl, C_{1-4} alkenyl, phenyl- C_{1-4} alkyl and phenyl (wherein the phenyl group in both cases is optionally substituted by one or more groups independently selected from C_{1-4} alkyl, C_{1-4} alkoxy, nitro, halo and trihalomethyl), C_{4-6} cycloalkyl, and 5- or 6-membered heterocyclic radicals containing at least one heteroatom selected from oxygen, sulphur and nitrogen; and Y^1 being a group selected from hydrogen, hydroxy, C_{1-4} alkoxy and C_{1-4} acyloxy; and salts and solvates thereof; which process comprises

(a) for the preparation of hydantoins wherein Z^2 is $-N=CH-R$, wherein R is as defined above, reacting a compound of formula (II) with a compounds of formula (III)

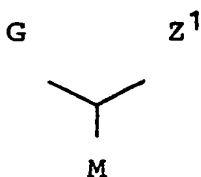


R-HCO (III)

(II)

wherein Z, Z' and R are as defined above, in, for example, the presence of a base and a suitable solvent, such as methanol;

(b) for the preparation of hydantoin wherein Z² is -N=CH-R, wherein R is as defined above, reacting a compound of formula (IV)



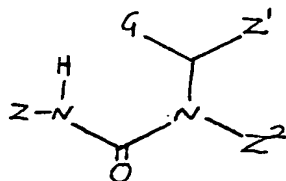
(IV)

wherein Z' is as defined above, G is carboxy or a derivative thereof, such as an amide derivative, for example, carbamoyl, or an ester thereof, particularly a C₁₋₄ alkyl ester thereof, or G is cyano, and M is a leaving group, such as halo, preferably bromo, with a compound of formula (V)

ZHNCONHN=CHR (V)

wherein R and Z are as defined above, in the presence of base in a polar solvent, such as ethanol;

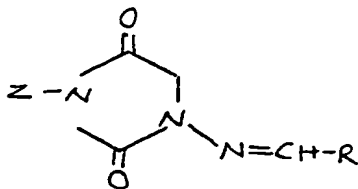
(c) for the preparation of hydantoin wherein Z² is =N=CH-R, wherein R is as defined above, cyclising a compound of formula (VI)



(VI)

wherein G, Z, Z' and Z² are as defined above, in, for example, the presence of acid or base or by heating in an inert solvent;

(d) for the preparation of hydantoin wherein Z² is -N=CH-R, wherein R is as defined above, treating a compound of formula (VII)

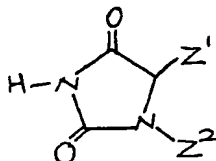


(VII)

wherein R is as defined above, with methyl magnesium carbonate followed by reaction in the presence of base with a compound of formula (VIII)

M-Z¹ (VIII)

wherein M and Z¹ are as defined above, in a non-protic solvent, such as THF or ether;
 (e) reacting a compound of formula (IX) with a compound of formula (X)



(IX)

wherein Z¹ and Z² are as defined above, L is a suitable leaving group, such as halo (eg bromine) or hydroxy, and Z³ is defined as for Z above (other than C₆ or C₁₀ aryl) or an alternative imino protecting group, for example, benzylideneamino (-N=CH-Ph), in the presence of base and, when L is hydroxy, triphenylphosphase and diethylazodicarboxylate;
 and subsequently, if desired, effecting one or more of the following optional conversions in any desired order:

i) where a hydantoin of formula (I) is formed and is an ester, converting said ester into the corresponding acid or a salt or solvate thereof;

ii) where a hydantoin of formula (I) is formed and is an acid, converting said acid into the corresponding ester or a salt or solvate thereof;

iii) where a hydantoin of formula (I) is formed wherein Z is hydrogen, converting said hydantoin into a corresponding hydantoin wherein Z is alkyl;

iv) where a hydantoin of formula (I) is formed wherein R is -CH(Y¹)Y, wherein Y¹ is an acyloxy group and Y is as defined above, converting said hydantoin into a corresponding hydantoin of formula (I) wherein Y¹ is a hydroxy group;

v) where a hydantoin of formula (I) is formed wherein R is -CO-Y, converting said hydantoin into a corresponding hydantoin wherein R is -CH(OH)-Y; or

vi) where a hydantoin of formula (I) is formed wherein Z² is -N=CH-R, converting said hydantoin into a corresponding hydantoin wherein Z² is -NH-CH₂-R, wherein R is as defined above.



EP 88 30 1474

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL 4)
D, X	EP-A-0 126 849 (THE WELLCOME FOUNDATION) * Whole document * -----	1, 4	C 07 D 233/80 A 61 K 31/415
			TECHNICAL FIELDS SEARCHED (Int. CL 4)
			C 07 D 233/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 31-05-1988	Examiner DE BUYSER I.A.F.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			